A Phase 2 Study of Daratumumab Subcutaneous (Dara-SC) Administration in Combination with Carfilzomib and Dexamethasone (DKd) Compared with Carfilzomib and Dexamethasone (Kd) in Participants with Multiple Myeloma who have been Previously Treated with Daratumumab to Evaluate Daratumumab Retreatment

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The purpose of this study is to compare the efficacy (rate of very good partial response [VGPR] or better as best response as defined by the International Myeloma Working Group [IMWG] criteria) of daratumumab subcutaneous (Dara-SC) in combination...

Ethical review	Approved WMO
Status	Completed
Health condition type	White blood cell disorders
Study type	Interventional

Summary

ID

NL-OMON55384

Source
ToetsingOnline

Brief title
LYNX

Condition

- White blood cell disorders

Synonym
Multiple Myeloma, plasma cell myeloma

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen-Cilag BV

Intervention

Keyword: Daratumumab, Multiple Myeloma, Retreatment, Subcutaneous

Outcome measures

Primary outcome

Primary objectives

The primary objective is to compare the efficacy (rate of very good partial response [VGPR] or better as best response as defined by the International Myeloma Working Group [IMWG] criteria) of Dara SC in combination with Kd with the efficacy of Kd in participants with relapsed refractory multiple myeloma who were previously exposed to daratumumab to evaluate daratumumab retreatment.

Primary Endpoint

The primary endpoint of this study is the rate of VGPR or better as defined by the IMWG criteria.

Secondary outcome

Secondary Objectives

The secondary objectives are:

To further characterize the efficacy (progression-free survival [PFS], overall survival [OS], overall response rate [ORR], rate of complete response [CR]/stringent complete response [sCR]) of Dara SC in combination with Kd

To evaluate the minimal residual disease (MRD) negativity rate and durability of MRD negativity status

To characterize the safety of Dara SC in combination with Kd

To determine time to next treatment

To evaluate the pharmacokinetics (PK) of Dara SC

To determine the immunogenicity of daratumumab and recombinant human hyaluronidase PH20 (rHuPH20)

Secondary Endpoints

The secondary endpoints are:

ORR (rate of partial response [PR], VGPR, CR, sCR)

Rate of CR/sCR

PFS

OS

MRD negativity rate

Time to next treatment

Serum daratumumab concentrations

Prevalence and incidence of anti-daratumumab antibodies and anti-rHuPH20

antibodies

Study description

Background summary

For relapsed or refractory multiple myeloma, the treatment is determined on an individual basis. Common standard of care regimens use either a proteasome inhibitor (PI) or an immunomodulatory agent (IMiD) in combination with dexamethasone with or without a monoclonal antibody (mAb) such as daratumumab. After relapse from PIs or IMiDs, patients are often retreated with drugs that have same mechanism of action to which they have been sensitive. The disease becomes refractory and all effective treatment options are exhausted. Daratumumab is a human IgG1 mAb that binds with high affinity to unique epitope on cluster of differentiation 38 (CD38) and attacks tumor cells that overexpress CD38. Study is to determine the efficacy of Dara-SC in combination with carfilzomib and dexamethasone (DKd) in adult participants with relapsed refractory MM who had 1 to 3 prior line(s) of treatment including a line containing Daratumumab to evaluate daratumumab retreatment. The MM treatment is determined on an individual basis where patient*s age, prior therapy, bone marrow function, co-morbidities, patient preference and time to relapse are considered. Common standard of care regimens use either PI or an IMiD in combination with dexamethasone with or without a mAb. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies including multiple myeloma. The study will be conducted in 3 phases: Screening (28 days), Treatment, and Follow-Up. Assessments like chest X-ray, spirometry test, electrocardiogram (ECG), will be performed during Screening phase. During the Treatment Phase, participants will be randomized to receive Kd or DKd. Efficacy assessments like bone marrow examination will be performed. Follow-up will continue until the end of study.

Study objective

The purpose of this study is to compare the efficacy (rate of very good partial response [VGPR] or better as best response as defined by the International Myeloma Working Group [IMWG] criteria) of daratumumab subcutaneous (Dara-SC) in combination with carfilzomib and dexamethasone (Kd) with the efficacy of

Kd in participants with relapsed refractory multiple myeloma who were previously exposed to daratumumab to evaluate daratumumab retreatment.

Study design

This is a Phase 2, open-label, randomized, multicenter study to determine the efficacy of DKd in adult participants with relapsed refractory multiple myeloma who had 1 to 3 prior line(s) of treatment including a line containing Daratumumab to evaluate daratumumab retreatment. Participants must have completed Dara IV at least 3 months prior to randomization. A target of 230 participants will be randomized in 2 treatment arms of 115 each. A diagram of the study design is provided in Section 1.2 Scheme.

The study will be conducted in 3 phases: Screening, Treatment, and Follow-Up. Screening begins at the time the participant provides written consent for study participation. During the Screening Phase, participants will be screened for study eligibility within 28 days prior to study randomization. All eligibility criteria must be met prior to starting study intervention.

During the Treatment Phase, participants will be stratified by prior PI exposure and daratumumab-free interval (3-6 months, >6 months) and then assigned randomly to receive Kd or DKd. Participants in both arms will receive study intervention until confirmed progressive disease (PD), death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first. Participants should start study intervention within 3 days after randomization. Participants will be closely monitored for AEs, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If disease progression is confirmed, then the participant will discontinue study intervention, complete the End-of-Treatment Visit, and enter the Follow up Phase.

Follow-up will continue until the end of study, no later than 2 years after the last participant has received their initial dose of study intervention or when the sponsor decides to stop the study. The sponsor will ensure that participants benefiting from treatment with Dara-SC continue to receive treatment after the end of the study.

Intervention

Participants will be treated with Kd alone (Arm A) or Dara SC in combination with Kd (Arm B) in 28 day cycles.

Study burden and risks

The combination of Kd with Dara SC is hypothesized to have a positive

benefit-risk profile when used for the treatment of patients with relapsed/refractory multiple myeloma who were previously exposed to Daratumumab. This hypothesis is based on the following:
Daratumumab responders who relapse may respond following a treatment break or by switching to a new daratumumab-containing combination regimen, as detailed in Section 2.2.
The Kd regimen to be used in this study has been approved for patients with relapsed or refractory multiple myeloma who had 1 to 3 prior line(s) of therapy (see Section 2.1.1).
The addition of daratumumab to the Kd regimen may improve initial disease control and long-term outcomes, based on data from an ongoing Phase 1b study (Study MMY1001) of the safety and efficacy of Dara IV with Kd (see Section 2.2).
Given the potential advantages of SC administration, Dara SC will be used in this study. As presented in Section 2.1.4 and the current daratumumab IB, the safety and tolerability of Dara SC has been demonstrated. Previous exposure-response analyses have demonstrated a strong correlation between ORR and the maximum daratumumab Ctrough. Analysis of the preliminary PK data indicated the 1800 mg Dara SC dose achieved maximum Ctrough values comparable with, or higher than, those observed for Dara IV 16 mg/kg as detailed in Section 4.2.
Considering the above, there is a strong rationale for evaluating Dara SC in combination with Kd for the treatment of relapsed refractory multiple myeloma patients previously exposed to Dara IV. More detailed information about the known and expected benefits and risks of daratumumab are provided in the IB.

Rationale for Subcutaneous Daratumumab

Subcutaneous administration of daratumumab has been chosen for this study to avoid the long infusion time that frequently requires hospitalization with Dara IV and to lessen the rate and severity of IRRs observed with Dara IV.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:
1. At least 18 years of age.
2. Documented multiple myeloma as defined by the criteria below: Measurable disease at screening as defined by any of the following: Serum M-protein level >=1.0 g/dL in participants with immunoglobulin G (IgG) type, or serum M-protein level >=0.5 g/dL in participants with non- IgG type, or urine M-protein level >=200 mg/24 hours; or Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain (FLC) >=10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.
3. Evidence of a response (partial response or better based on investigator*s determination of response by IMWG criteria) to daratumumab-containing therapy with response duration of at least 4 months.
4. Relapsed or refractory disease as defined below: Relapsed disease is defined as an initial response to previous treatment, followed by confirmed PD by IMWG criteria >60 days after cessation of treatment. Refractory disease is defined as <25% reduction in M-protein or confirmed PD by IMWG criteria during previous treatment or <=60 days after cessation of treatment.
5. Received 1 to 3 prior line(s) of treatment of which one contained Daratumumab and completed Daratumumab at least 3 months prior to randomization. A single line of therapy may consist of 1 or more agents, and may include induction, hematopoietic stem cell transplantation, and maintenance therapy. Radiotherapy, bisphosphonate, or a single short course of corticosteroids (no more than the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy.
6. ECOG Performance Status score of 0, 1, or 2.
7. Pretreatment clinical laboratory values meeting the following criteria

during the Screening Phase:
a) hemoglobin >=8 g/dL (>=5mmol/L) (without prior RBC transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted);
b) absolute neutrophil count (ANC) >=1.0 × 10^9/L (prior growth factor support is permitted but must be without support within the 7 days prior to the laboratory test);
c) platelet count >=75 ×10^9/L for participants in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count of >=50×10^9/L. Transfusions are not permitted within 7 days of testing to achieve this minimum platelet count.
d) aspartate aminotransferase (AST) <=2.5 × upper limit of normal (ULN);
e) alanine aminotransferase (ALT) <=2.5 × ULN;
f) total bilirubin <=1.5 × ULN; except in participants with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin <=1.5× ULN is required);
g) estimated creatinine clearance (CrCl) >=20mL/min per 1.73m^2. CrCl to be calculated using estimated glomerular filtration rate Modification of Diet in Renal Disease (MDRD) formula.
h) albumin-corrected serum calcium <=14 mg/dL (<=3.5 mmol/L) or free ionized calcium <=6.5 mg/dL (<=1.6mmol/L)
8. Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy.
9. Women of childbearing potential must have a negative urine or serum pregnancy test at screening within 14 days prior to randomization.
10. Each participant must sign an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Participants must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF

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Exclusion criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

2. Previous treatment with carfilzomib.
3. Previous treatment with daratumumab within the last 3 months prior to randomization.
4. Discontinuation of Daratumumab due to a daratumumab-related AE.
5. History of malignancy (other than multiple myeloma) unless all treatment of that malignancy was completed at least 2 years before consent and the patient has no evidence of disease. Further exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or breast, or other non-invasive lesion, that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years.
6. Allergies, hypersensitivity, or intolerance to daratumumab, hyaluronidase, mAbs, human proteins, or their excipients (refer to the IB), or known sensitivity to mammalian derived products. Known history of allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib).
7. Contraindications to the use of any components of the backbone treatment regimens, per local prescribing information.
8. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before randomization (except for investigational anti-myeloma treatments, which cannot be taken within 2 weeks or 5PK half-lives of the treatment from the first dose of daratumumab, whichever is longer, before the date of randomization).
9. Pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study intervention.
10. Plans to father a child while enrolled in this study or within 3 months after the last dose of study intervention.
11. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
12. Received anti-myeloma treatment within 2 weeks or 5 PK half-lives of the treatment from the first dose of daratumumab, whichever is longer, before the date of randomization. The only exception is emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 mg/day for a maximum of 4 days) up to 21 days before treatment. A list of anti-myeloma treatments with the corresponding PK half-lives is provided in the Site Investigational Product Procedures Manual.
13. Received autologous stem cell transplant within 12 weeks before the date of randomization, or the participant has previously received allogeneic stem cell transplant (regardless of timing).

14. Plans to undergo a stem cell transplant prior to progression of disease on this study.
15. Focal radiation therapy within 14 days prior to randomization with the exception of palliative radiotherapy for symptomatic management but not on measurable extramedullary plasmacytoma. Radiotherapy within 14 days prior to randomization on measurable extramedullary plasmacytoma is not permitted even in the setting of palliation for symptomatic management.
16. Clinical signs of meningeal involvement of multiple myeloma.
17. Either of the following:
a) Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) is <50% of predicted normal. Note that FEV1 testing also is required for participants suspected of having COPD and participants must be excluded if FEV1 is <50% of predicted normal.
b) Known moderate or severe persistent asthma, or a history of asthma within the last 2 years, or currently has uncontrolled asthma of any classification. (Participants who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.)
18. Participant is:
a) known to be seropositive for human immunodeficiency virus (HIV), with 1 or more of the following:
i. Not receiving highly active antiretroviral therapy (ART)
ii. Had a change in ART within 6 months of the start of screening
iii. Receiving ART that may interfere with study treatment (consult Sponsor for review of medication prior to enrollment)
iv. CD4 count <350 at screening
v. Acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within 6 months of start of screening
vi. Not agreeing to start ART and be on ART >4 weeks plus having HIV viral load <400 copies/mL at end of 4-week period (to ensure
ART is tolerated and HIV controlled)
b) seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Participants with resolved infection (ie, participants who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR (See Appendix 16).
c) known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).
19. Concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease, pulmonary hypertension) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard

for participating in this study.
20. Uncontrolled hypertension, defined as an average systolic blood pressure >159mmHg or diastolic >99 mmHg despite optimal treatment (measured following European Society of Hypertension/European Society of Cardiology 2013 guidelines).
21. Clinically significant cardiac disease, including:
Myocardial infarction within 6 months before date of randomization, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV; Appendix 12).
Uncontrolled cardiac arrhythmia (Grade 2 or higher by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 4.03) or clinically significant electrocardiogram (ECG) abnormalities.
Transthoracic echocardiogram or MUGA scan showing left ventricular ejection fraction <40%.
22. Gastrointestinal disease that may significantly alter the absorption of oral drugs.
23. Myelodysplastic syndrome, plasma cell leukemia (>2.0 × 109/L circulating plasma cells by standard differential) or Waldenström's macroglobulinemia or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) or amyloidosis.
24. Not able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder) or the participant has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments.
25. Major surgery within 2 weeks before randomization, or has not fully recovered from an earlier surgery, or has major surgery planned during the time the participant is expected to participate in the study or within 2 weeks after the last dose of study intervention administration. Kyphoplasty or vertebroplasty are not considered major surgery. Note: participants with planned surgical procedures to be conducted under local anesthesia may participate. If there i

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	31-07-2019
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Darzalex
Generic name:	Daratumumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Decadron
Generic name:	Dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Kyprolis
Generic name:	Carfilzomib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-04-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-06-2019
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	06-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-004185-34-NL
CCMO	NL69472.056.19

Study results

Date completed:	12-10-2022
Results posted:	08-01-2024

Summary results
Trial ended prematurely

First publication
28-10-2023

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File